AD 682581

TRANSLATION NO. 412

DATE: July 1968

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DEPARTMENT OF THE ARMY
Fort Detrick
Frederick, Maryland

AD 682581

# EPICUTANEOUS SKIN TEST WITH TULARIN FROM VACCINE STRAIN TO DETERMINE IMMUNITY IN THOSE INOCULATED AGAINST TULAREMIA AND FOR DIAGNOSIS OF THIS INFECTION

(Nakozhnyi tuliarin iz vaktsinnogo shtamma dlia opredeleniia immuniteta u privitykh protiv tuliaremii i diagnostiki etoi infektsii)

Voprosy Epidemiologii i Profilaktiki Tuliaremii [Problems of Epidemiology and Prophylaxis of Tularemia], book edited by Professor N. G. Olsuf'yev et al., Medgiz-Moscow, 1958, pages 156-158

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For the purpose of determining the immunity in those who have been inoculated against tularemia, and for the diagnosis of this disease, tularin, injected intracutaneously, is being extensively used as an antigen. The preparation contains 100,000,000 microbe cells (according to the optical microbial standard) in one cubic centimeter; the dose of preparation injected is 0.1 cubic centimeter, which amounts to 10,000,000 microbe cells.

The high degree of specificity of the intracutaneous tularin test and its diagnostic value in tularemia are generally known.

However, it also is known that tularin by intracutaneous injection causes undesirable side reactions in a number of cases, and particularly in those who have had tularemia.

According to I. N. Mayskiy's (1953) data, in the examination of those tested nine months after vaccination, tissue necrosis was noted at the site of tularin injection in 10 percent of the persons; in three percent there was a chill with an elevation of temperature to 38°; in 14 percent--malaise and headaches; in 29 percent, induration and a slight enlargement of the regional lymph nodes.

In the search for a preparation which gives fewer side reactions, and is more convenient for practical use, A. A. Vol'ferts, in 1934, suggested epicutaneous tularin for the diagnosis of tularemia. Afterwards, the investigators (L. M. Khatenever, 1941; A. N. Berinskaya and M. V. Afanas'yev, 1940) confirmed the diagnostic value of the epicutaneous tularin test, but the preparation was not adopted into general practice. N. A. Popov and his associates (1953) clarified the possibility of utilizing the epicutaneous tularin test for detection of the allergic state in persons vaccinated against tularemia.

In the large-scale use of ordinary tularin, for the detection of the immune segment among the population of the Volga-Akhtubinsk River Valley, we also ran up against the excessive reaction-producing capacity of this preparation, and against certain technical inconveniences in its use associated with the strictly intracutaneous application. This caused us to occupy ourselves with the

study of epicutaneous tularin and to determine to what extent it could be substituted for intracutaneous tularin.

In our preceding work (N. G. Olsuf'yev, V. P. Borodin, N. S. Surnina and Ye. M. Tsvetkova) it was shown that tularin prepared from virulent, vaccine, and avirulent strains of tularemia bacteria brings about the occurrence of a completely distinct allergic reaction, 24-48 hours after its epicutaneous use, both in those who have had tularemia and in those who have been inoculated against this disease. This tularin contained 2,000,000,000 microbial cells per cubic centimeter according to the GKI [*State Control Institute]. The allergy was expressed in the appearance of hyperemia and infiltration involving an area of skin from 0.5 to two centimeters (rarely more) in diameter. The preparations made from the virulent or the vaccine strains proved to be equivalent in the diagnostic sense, whereas tularin from the avirulent strain was somewhat inferior to them in a small number of cases. In contrast to ordinary intracutaneous tularin, the epicutaneous tularin produced practically no side effects. Of the 100 persons examined, an insignificant malaise lasting several hours, was noted the day after the tularin administration, in only one person who had had the disease, and in two who had been inoculated. We did not observe necrosis at the

*Gosudarstvennaia konservnaia inspektsiia (State Inspection of Canned Food - the Soviet equivalent of our Food and Drug Administration)

site of administration of the preparation, or enlargement, or tenderness of the lymph nodes in a single case.

Considering that the production of tularin from the vaccine strain is much simpler than that from the virulent strain, we decided to extend the testing of this variant in order to bring about its adoption into practice. To obtain completely objective data, medical personnel from tularemia stations were brought together for a project of mass tularin skin testing. The Stalingrad (V. P. Borodin, A. P. Koroleva), Voronezh (I. G. Khoroshev, V. S. Sil'chenko), Tula (Yu. A. Myasnikov, Z. A. Perfil'yeva), Plavsk (N. Y. Kratokhvil', M. A. Vaystikh), Omsk (O. V. Ravdonikas, N. N. Baranova, V. Ye. Zimina), Krasnodar (L. N. Tormasova, T. F. Ustin-Petrova), Moscow (S. S. Aref'yev, N. S. Konkina, A. P. Kul'ba, N. K. Mal'tseva, G. M. Shelanova) and Smolensk (A. M. Sorina, V. S. Branitskaya, M. N. Prudnikova) Stations participated in this.

The tularin was prepared by the Tularemia Laboratory of the Institute of Epidemiology and Microbiology, Academy of Medical Sciences USSR, (Ye. M. Tsvetkova) by the usual method.

For this study, two variants of the epicutaneous tularin, from the vaccine and virulent strains, were used.

Extensive testing with both variants, carried out on 3958 inoculated persons and 212 persons who had had tularemia, completely confirmed the high degree of effectiveness of the epicutaneous tularin from the vaccine strain, and that it was not inferior to that prepared from the virulent strain.

The majority of inoculated persons (in this group) were examined one to three years after the epicutaneous vaccination, and part of them, after four or more years. Those who had had the disease were examined at various intervals after the disease--from one to 10 years or more. Epicutaneous tularin demonstrated the allergic state well in persons who had been inoculated one or two years previously, as well as in persons who had been inoculated eight or nine years previously. Those who had had the disease reacted to tularin in practically all cases. Among those inoculated, side effects from the epicutaneous tularin were noted in 2.5-2.8 percent, whereas among those who had had the disease they were noted in 20-22 percent. However, in both groups these side effects were completely tolerable and brief. They usually were expressed in a brief (several hours) period of malaise, and less often, in an insignificant temperature rise, or in a transitory moderate enlargement of the axillary lymph nodes. No necroses were found at the site of the tularin skin test.

Large-scale testing with the epicutaneous tularin confirmed the need for a 48-hour interval for the purpose of reading the skin reaction.

In two rayons of the Volga-Akhtubinsk River valley we studied the possibility of application of epicutaneous tularin (from a virulent strain) for mass skin testing of the population with the aim of identifying the segment immune to tularemia. For this purpose, 1234 persons in 11 inhabited places were tested in the Stepno-Akhtubinskiy and Krasnoslobodskiy Rayons in February and March 1954.

(A. P. Koroleva participated in the investigation). These places were located deep in the river valley, they attracted our attention because we were not sure of the immunization status of their populations.

Special attention was given to the technic of performing the tularin skin test, which consisted of the following: a single drop of tularin was applied to the skin of the middle third of the arm (previously cleansed with alcohol) and two parallel incisions 0.8-one centimeter in length (at a distance of 0.4-0.5 centimeters from each other) were made on the skin through the drop with a scarificator. We considered it essential that blood ooze slightly from the incisions (tiny drops). The drop of tularin on the incisions was rubbed in for a short time with the flat side of the scarificator.

The vaccination in these two rayons was carried out during the period from 1948 through 1953, that is, one to six years before the checking, the majority of the inoculations were done in 1951-1952. In this group, 652 persons had a record of a successful inoculation. Of these, 494 persons, or 75%, reacted to the epicutaneous tularin. The highest percentage of reactors was noted among those inoculated one or two years previously (78-86 percent). Twenty-three persons were recorded as having had tularemia in the past, they all reacted to tularin without exception. Among the other 559 persons without a record of a successful immunization, or of having had the disease, 128 persons, or 23 percent, reacted to the epicutaneous tularin. Apparently, this was the result of an inaccurate recording of the results of the inoculations (omissions of positive reactors) or,

which is less probable, of the inadequate identification of persons who had previously had tularemia.

The results of this skin testing showed 52% of the total population immune to tularemia, a fact proving the need for supplementary vaccination of previously covered population groups.

On the basis of the mass skin testing performed, as well as that performed under our direction by workers of the tularemia stations, epicutaneous tularin from the vaccine strain may be characterized as a very convenient and highly effective diagnostic preparation, without too many side effects, which frequently accompany the use of intracutaneous tularin.

## CONCLUSIONS

1. Epicutaneous tularin from the vaccine strain is entirely suitable for detecting the allergic state in those inoculated against tularemia, at various intervals after the vaccination and revaccination, as well as in persons who have had tularemia in the past.

2. Epicutaneous tularin produces a weaker reaction than the intracutaneous tularin, and fewer side effects, in persons who have been inoculated against, or who have had tularemia.

3. In the mass population testing , epicutaneous tularin has justified itself as a completely specific test, technically much easier to perform than the intracutaneous test.

4. Epicutaneous tularin is entirely suitable for mass testing inhabitants, in natural foci of infection areas, who have submitted to some degree of vaccination, for the purpose of identifying the immune segment.